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ANATOMY OF THE HYPOTHALAMUS
AND ITS CONNECTIONS

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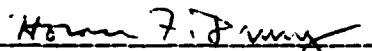
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ABSTRACT

This report briefly summarizes hypothalamic anatomy in terms of boundaries, cellular groups, intra, efferent and afferent connections, and ontogenetic development. Wherever possible, discussion is directed or limited to aspects of hypothalamic anatomy that are of special significance to the nervous control of shivering. For this reason the connections between the septal area of the forebrain and the hypothalamus are emphasized.

PUBLICATION REVIEW

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ANATOMY OF THE HYPOTHALAMUS
AND ITS CONNECTIONS*

The hypothalamus is that basal region of the brain that surrounds the
ventral aspect of the third ventricle in immediate proximity to the pituitary
gland with which it has intimate nervous, vascular and functional relations.
Its bilateral volume is but 216 mm^3 in the cat and takes up but three per
cent of the total human brain weight (Mitchell, 1953). Mitchell stated in
1953 that "anyone who suffers from the delusion that anatomy is an effete
subject with no problems left to solve is advised to read but a little of the
bewildering conglomeration of literature on the hypothalamus and its con-
nections. If he does so, delusion will be replaced with disillusion." An
attempt is here made to briefly summarize hypothalamic anatomy in terms
of its neuroanatomical boundaries, its cellular groups, intra, efferent and
afferent connections, and ontogenetic and comparative aspects of its devel-
opment. Wherever possible, discussion is directed or limited to aspects
of hypothalamic anatomy that are of special significance to the nervous
control of shivering.

A. Hypothalamic Boundaries and Nuclei

1. Boundaries

Only the medial boundary, the layer of ependymal cells that surround
the third ventricle and the ventral one, the base of the brain, are well
defined. Rostrally the hypothalamus is bounded by the lamina terminalis, a
thin plate of tissue between the anterior commissure and the optic chiasma
that reflects the closing plate of the primitive neural tube. Rostrolaterally
it merges with the telencephalon's preoptic region, there being no embry-
onic, phylogenetic or functional reason to propose a clear separation
between these two regions. Dorsally it is bounded by the hypothalamic
sulcus, a lateral extrusion of the third ventricle. This sulcus is more
prominent in the embryonic brain and is considered by some but not all
anatomists to be the rostral continuation of the sulcus limitans (Clark et al,
1938). It is not here the purpose to debate this issue but since in the prim-
itive or embryonic brain the sulcus limitans separates the dorsal, function-
ally affective alar plate from the ventral, functionally effective basal plate of

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nervous tissue, it is obvious that any consideration of the hypothalamic sulcus being the rostral continuation of the sulcus limitans has no functional justification, since hypothalamic activity embraces both affective and effective phenomena.

Caudally the hypothalamus passes without any sharp demarcation into the midbrain tegmentum and its caudal boundary is defined as a plane from the posterior margin of the mammillary body ventrally to the habenular-peduncular tract dorsally. As with the rostral limit, this boundary cannot be defended on embryonic, phylogenetic or functional grounds.

Laterally the hypothalamus merges with the subthalamus, which includes the zona incerta, the fields H_1 and H_2 of Forel, the nucleus of the fields of Forel, the subthalamic nucleus and nucleus of the ansa lenticularis. Apparently anatomists up to 20 years ago (Clark et al, 1938) divided the tissue ventral to the thalamus into hypo- and subthalamus purely on functional grounds in that it was considered that the hypothalamus was concerned with effective visceral functions in its relation to the pituitary gland and medial forebrain bundle, whereas the subthalamus seemed, in its relations to the lateral forebrain bundle (the pathway connecting the basal ganglia and neocortex with the brainstem), more involved with the control of the skeletal musculature. On these grounds the demarcation is no longer tenable. Both hypothalamus and subthalamus affect visceral and somatic activities. In this review, however, the demarcation is accepted in respect, but not defense, of classical anatomy.

The boundary between medial and lateral hypothalamus is considered to be a vertical plane joining the mammillothalamic tract dorsally and the fornix ventrally. Hypothalamic regions medial to this plane contain more cells than fibers. The reverse is true for those regions lateral to this plane.

2. Nuclei

In defining the principal nuclei of the hypothalamus it is conventional to divide them as belonging to four anterior-posterior regions, as shown below.

a. Preoptic region

Medial Preoptic Nucleus (vaguely defined clump of small cells — adjacent to this ventricle).

Lateral Preoptic Nucleus (medium sized cells — diffusely scattered in medial forebrain bundle — direct rostral extension of lateral hypothalamus nucleus).

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b. Supraoptic Region

Supraoptic Nucleus (large cells straddling optic chiasma and commencement of optic tract in close relation to ventral pia mater).

Paraventricular Nucleus (largest cells in hypothalamus form vertical band from optic chiasma to ventral medullary laminar of thalamus - in its dorsal extremity merges laterally with zona incerta of subthalamus).

Suprachiasmatic Nucleus (small midline cells dorsal to optic chiasma — immediately caudal to medial preoptic nucleus).

Anterior Hypothalamic Nucleus (scattered cells so undifferentiated and ill defined that perhaps better called a region - immediately caudal to suprachiasmatic nucleus and rostral to tuberal region — bounded medially by periventricular cells and laterally by medial forebrain bundle).

c. Tuberal Region

Dorsomedial Nucleus (small cells, adjacent to third ventricle and merging laterally with zona incerta of subthalamus).

Ventromedial Nucleus (dense group of well defined but small cells — bears closest topographic relation to pituitary gland of all hypothalamic nuclei).

Arcuate Nucleus (small midline cells ventromedial to ventromedial nucleus — extending caudally into intramammillary recess).

Posterior Hypothalamic Nucleus (a junctional region of loosely collected cells between tuberal region, mammillary bodies and reunions nucleus of thalamus).

d. Mammillary Region

Medial Mammillary Nucleus (large ventrosuperficial mass of large cells).

Lateral Mammillary Nucleus (small zone of smaller but sharply defined cells immediately adjacent to third ventricle.

Intercalate Nucleus (diffusely scattered small cells immediately lateral to lateral mammillary nucleus).

Premammillary Nucleus (immediately rostrodorsal to medial mammillary nucleus — poorly differentiated from posterior hypothalamic nucleus).

Two additional nuclei, fitting no particular anterior-posterior zone, are described in the literature (Mitchell, 1953). First is a lateral hypothalamic nucleus which is considered to be an interstitial nucleus in that its cells are sparsely arranged within the medial forebrain bundle and hence populate the entire length of the lateral hypothalamus. The cells are larger but the nucleus diminishes in width in the posterior as compared to the anterior hypothalamus. Second is the perifornical nucleus, a group of cells surrounding and compressed by the fornix in its postcommissural course to the mammillary body; hence the nucleus traverses the entire length of the midhypothalamus.

Of all the above nuclei only the supraoptic, paraventricular and mammillary nuclei stand out in terms of their size, and in the case of the former two, in terms of their greater density of capillary networks and specific functions, osmoreception (Cross and Green, 1959) and neurosecretion (Hild, 1956).

The rest of the nuclei of the hypothalamus are fused into a reticulum with myelinated and unmyelinated fibers, which stream transversely, dorsally, ventrally, and caudally. The names of the nuclei are presented only for purposes of orientation because, with the exception of the supraoptic and paraventricular nuclei, no specific function or individual anatomical character can be ascribed to them. As recently pointed out by Ingram (1959), at our present stage of knowledge of the physiology of the hypothalamus, functions are best ascribed to regions rather than specific hypothalamic nuclei.

B. Intra and Efferent Hypothalamic Connections

1. Intra Hypothalamic Connections

Certain commissures course across the hypothalamus uniting the right and left sides of the brain. To varying extents they unite hypothalamic regions as follows.

a. Supraoptic Commissures

This is a well defined commissure that crosses the midline ventral to the third ventricle and dorsal to the optic chiasm. The most dorsal part of this commissure is called Ganser's commissure, the midportion Meynert's commissure and the most ventral part is termed Gudden's commissure. Ganser's commissure arises in the fasciculus lentricularis and is separated by the post-commissural fornix into a medial and lateral fascicle. The medial fascicle crosses the midline to terminate in the ventromedial nucleus of the tuberal region but has ipsilateral connections in or near the ventromedial nucleus. It is somewhat caudal to Meynert's

commissure and crosses the midline to terminate in the medial forebrain bundle, the subthalamus and the pyriform lobe of the cerebral hemisphere. Meynert's commissure originates in the rostral globus pallidus and crosses the midline to terminate in the zona incerta and the medial forebrain bundle. Ingram (1939) could find no evidence of these tracts forming specific connections between hypothalamic nuclei except by secondary projections within the medial geniculate bodies and possibly the inferior colliculi. This commissure is more predominate in lower mammals.

b. Supramammillary Decussations

Supramammillary decussations occur rostral to mammillary bodies and ventral to the third ventricle. The fibers arise primarily from three sources. Periventricular fibers cross the midline to terminate immediately ventral and lateral to the midbrain aqueduct. Fornical fibers cross the midline to terminate in the midbrain tegmentum, possibly without synapsing in the hypothalamus (Nauta, 1958; Sprague and Meyer, 1950). Finally supramammillary nucleus fibers cross the midline to terminate in the interpeduncular nucleus of the midbrain.

Apart from these contralateral connections there are relatively well defined ipsilateral intrahypothalamic connections as follows.

c. Paraventricular-Supraoptic and Supraoptic-Tuberal Connections

These connections are both part of the hypothalamic-hypophyseal system, which, since not related to the nervous control of shivering, will not be discussed in this text.

d. Residual Fasciculus

This tract runs with the optic tract (persists after completed optic tract degeneration) and interconnects the supraoptic and lentiform nuclei. It might better be termed an efferent hypothalamic projection.

e. Medial Forebrain Bundle

This tract arises in the olfactory bulb tract and tubercle, forebrain septum, anterior head of the caudate and amygdala nuclei, nucleus of the diagonal band of Broca (interconnecting amygdala and septum) and the anterior part of the hippocampus. It courses through the lateral hypothalamus to terminate in the midbrain tegme..tum, containing in its hypothalamic course the cells of the lateral hypothalamic nucleus. Its route through the hypothalamus is lateral rostrally (i. e., lateral to the fornix and the mammillothalamic tract) and ventrolateral caudally (i. e., between the cerebral peduncle and the mammillary body). In the course of its hypothalamic path it receives from and projects to all hypothalamic nuclei.

By connecting the rhinencephalon to the midbrain, McLean (1949) has postulated its role as homologous to that of the internal capsule which connects the neocortex to the midbrain. The potential intrahypothalamic connections within this bundle seem unlimited.

2. Efferent Hypothalamic Connections

There are eight established systems of efferent hypothalamic projections which can be grouped as follows.

a. Efferent Mammillary Tracts

Arising from the mammillary bodies is a principal mammillary tract which bifurcates to project rostrally to the anterior thalamic nucleus as the mammillothalamic tract and caudally to the central tegmental nucleus of the midbrain, as the mammillo-tegmental tract.

The anterior thalamic nucleus has two-way connections with the cingulate gyrus, which when stimulated evokes some motor and visceral effects (Smith, 1945; Ward, 1948). There are allegedly (Clark, 1932) also two-way connections between the mammillothalamic and the anterior thalamic nuclei but when the mammillothalamic tract is stimulated (Sigrist, 1945) it does not evoke motor and visceral effects; so it would appear that cingulate gyrus hypothalamic connections other than this tract mediate visceral and motor effects. Cajal (1911) thought the mammillothalamic tract was formed from mammillo-tegmental tract collaterals but von Vankenberg (1911) proposed these tracts arise from separate medial mammillary nucleus cells. However, more recently Guillery (1955) has counted the rabbit and cat medial mammillary nucleus cells, the principal mammillary tract fibers and the mammillothalamic tract fibers and found them to be equal, but to my knowledge no one has counted the number of fibers in the mammillo-tegmental tract. Until this information is available, it would appear difficult to postulate the manner in which the principal mammillary tract bifurcates into mammillothalamic and mammillo-tegmental tracts.

Koelliker (1896), Simson (1952), Daitz (1953), Rose (1939-40) and Guillery (1955) have all proposed that the higher the brain in phylogeny, the larger the mammillary bodies (receiving a greater number and percentage of post-commissural fornical fibers), and the larger the mammillothalamic tract in comparison to the mammilo-tegmental tract. This latter tract is quite small in men. It is doubtful that the mammillo-tegmental tract could be implicated in the production of shivering.

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b. Hypothalamico-Hypophyseal Tracts

These tracts are well reviewed by Mitchell (1953) and Green (1956). Since the pituitary gland is not implicated in the production of shivering they will not be discussed.

c. Periventricular Tracts

These tracts consist of predominantly non-myelinated fibers, immediately adjacent to the third ventricle's ependyma. The fibers allegedly arise from most hypothalamic nuclei and in the rostral hypothalamus stream vertically to form two-way connections with dorsomedial thalamic nuclei and from the caudal hypothalamus stream horizontally to connect the hypothalamus with midbrain fasciculi. Earlier anatomists, e. g. Krieg (1932) and Rogers and Wheat (1921), believed this vertical periventricular projection was of little consequence. Guillery (1959) has recently presented evidence that there is no direct hypothalamic projection to the dorsomedial thalamic nucleus. Since the dorsomedial nucleus and the thalamus are not implicated in the production of shivering, the periventricular tract's caudal projections are more important here.

There are three major midbrain tracts by which these caudally projecting fibers could influence the spinal cord.

i. Dorsal Longitudinal Fasciculus. This tract was first described by Schutz in 1891 and is reviewed by Mitchell (1953); later works restricted it to a tract originating from hypothalamic periventricular fibers streaming ventral to the midbrain aqueduct, joining the medial longitudinal fasciculus at the floor of the fourth ventricle to descend into the spinal cord within the anterior column's fasciculus proprius and hence to impinge upon the lateral gray column of the thorac-lumbar segments. However, Ranson and Magoun (Magoun, 1939; Magoun et al, 1938) believed this tract to have a far broader spinal cord distribution and termination.

ii. Medial Longitudinal Fasciculus. This tract arises from the periventricular system via the interstitial nucleus of the midbrain, a small group of cells on the lateral walls of the third ventricle, immediately dorsal to the midbrain aqueduct. It joins the dorsal longitudinal fasciculus on the floor of the fourth ventricle, being posterior to the aqueduct in its descent. It probably forms a major component of the spinal cord's fasciculus proprius, but exact terminations are not known.

iii. Hypothalamic Reticulo-Spinal Connections. This tract is not widely accepted by anatomists, but in 1932 Allen reported short periventricular fibers as terminating in the midbrain reticular formation with secondary spinal cord projections in the reticulo-spinal tract.

d. Diffuse Descending Connections

Ranson and Magoun (Magoun, 1939; Magoun et al, 1938) clas-
sified such connections as arising from all the hypothalamic nuclei, joining
the medial forebrain bundle laterally and then terminating diffusely in the
midbrain reticulo-formation with secondary projections to all the descending
extrapyramidal tracts. Mitchell (1953) felt that such connections could be
classified as hypothalamic-reticulo spinal but since they do not arise from
the periventricular fibers and do not descend solely in the reticulo-spinal
tract, it would seem a somewhat restrictive term.

Much debate exists along all the above information, best
reviewed by le Gros Clark et al (1938) Ingram (1939) and Mitchell (1953).
None of the presented evidence illustrates hypothalamic connections specif-
ically innervating alpha motor horn cells of the spinal cord. Nonetheless
it is suitable to illustrate the possibility that activation of an ipsilateral
hypothalamic region could evoke both ipsi and contralateral motor horn cell
activity. It should further be obvious that even if the specific extra-
pyramidal tracts involved in the production of shivering were known, which
they certainly are not (Birzis, 1955), it would still be impossible to deduce
their hypothalamic origins on the basis of the above data.

C. Afferent Hypothalamic Connections

In reviewing known connections impinging on the hypothalamus, more
emphasis is placed on those tracts that might possibly play roles in the
modulation of shivering.

1. Mammillary Peduncle

This bilateral tract, quite inconspicuous in man, is formed in the
midbrain and projects rostrally around the interpeduncular nucleus to
terminate in the intercalate and mammillary nuclei. The origin of its
fibers is obscure. Le Gros Clark et al (1938) surmised some of its fibers
arose in gustatory and visceral nuclei of the 9th and 10th cranial nerves.
Fox (1941) believed its origin to be the ventral tegmental nuclei, while
others (Mitchell, 1953) considered the tract formed from fibers detaching
from the main bundle of the adjacent medial lamniscus and from afferent
visceral fibers accompanying the lemniscal tracts. Gurdjian (1927) and
others (Mitchell, 1953) have suggested that a proportion of its fibers extend
more rostrally to other hypothalamic nuclei.

2. Vago-Hypothalamic Connections

In keeping with the above, such connections may travel within the
mammillary peduncle. In 1932 Papez reported degeneration within the

following vagal nuclei destruction in the opossum. Electrophysiological evidence of Bronk and coworkers (1936) indicated supraoptic nuclei potentials evoked during vagus nerve stimulation in the cat. Bailey and Brewer (1938) demonstrated EEG changes predominantly in area 13 (within orbital gyrus of cortex) of the cat during vagus nerve stimulation. Since there are known two-way connections between the orbital gyrus and the hypothalamus it is not known if vago-hypothalamic connections are direct or indirect via the orbital gyrus. No one has simultaneously recorded from area 13 and the supraoptic or any other hypothalamic nuclei during vagal stimulation.

3. Thalamic-Hypothalamic Connections

These include the mammillo-thalamic and periventricular tracts which, as described above, form two-way connections. It is significant that there is little mention or proof in the literature of direct connections between the hypothalamus and the ventroposterolateral thalamic nucleus (which as described elsewhere is considered but not proved to be the locus of skin temperature afferent fiber termination). Mitchell (1953) has assumed that such connections travel with the periventricular system, but since the ventroposterolateral thalamic nucleus is not immediately adjacent to the third ventricle it would seem a more specific tract must be localized before accepting this assumption.

Although in the above three tracts there is no direct evidence of hypothalamic reception of skin temperature fibers, it would appear that they could impinge upon the hypothalamus via the mammillary peduncle and/or vagohypothalamic connections without prior thalamic relay.

4. Optic-Hypothalamic Connections

In 1947 Frey reported that following enucleation of one or both eyes of a guinea pig and subsequent secondary degeneration of optic roots, degeneration was evident in both the ipsi and contralateral periventricular region immediately ventral to the rostral margin of the tuberal region's ventromedial nucleus. This work has never been verified and it is not known if the degeneration seen by Frey in the hypothalamus was a result of a direct optic-hypothalamic tract or if it was due to degeneration of an optic-lateral geniculate-hypothalamic tract.

5. Cerebellar-Hypothalamic Connections

In reviewing the physiology of the cerebellum, Moruzzi (1950) has pointed out that cerebellar stimulation influences autonomic activity. It is known that the majority of cerebellar efferents terminate in the midbrain (red nucleus) and that some further project via the fields of Forel to the thalamus (Mitchell, 1953). It is not known if there are cerebellar

connections with the hypothalamus via the fields of Forel, but such a speculation seems quite plausible. On the other hand, perhaps cerebellar stimulation alters autonomic action via middle and inferior cerebellar peduncle efferents that, in a way as yet undescribed, may impinge upon pontile and bulbar nuclei related to autonomic function.

6. Pallido-Hypothalamic Connections

There are well established widespread connections between the basal ganglia and the hypothalamus that arise primarily in the globus pallidus and connect with the majority of hypothalamic nuclei by way of the medial forebrain bundle, the zona incerta and the subthalamic nucleus. As such the concept of a specific subthalamic-hypothalamic connection would seem better considered as a part of the pallido-hypothalamic system of fibers. However, certain subthalamic-hypothalamic fibers are considered to relay lateral and medial geniculate (optic and auditory) information to the hypothalamus.

7. Telencephalo-Hypothalamic Connections

a. <u>Amygdala-Hypothalamic Connections</u>

These connections have very recently been reviewed by Wendt (1960) and may be summarized as follows.

i. Stria Terminalis. This tract originates in the medial amygdaloid nuclei, runs posterior to the internal capsule, thence dorsolateral to the ventrolateral preoptic region, the paraventricular and possibly other hypothalamic nuclei.

ii. Longitudinal Association Bundle. This tract receives fibers from the basolateral amygdaloid complex and the periamygdaloid cortex and extends rostralward to terminate in the ventral preoptic region and the medial forebrain bundle.

iii. Diagonal Band of Broca. This tract runs rostroventromedialward from the amygdala to the pyriform cortex, olfactory tubercle and septum. It was considered by the older anatomists to contain two-way connections but this has never been confirmed experimentally, and recent reviews by Ban and Omakai (1959) and Hall (1960) have not included this tract as an efferent amygdaloid projection. If such two-way connections exist, this tract would connect the amygdala to the hypothalamus by way of the medial forebrain bundle and the septum.

iv. Direct Diffuse Connections. This system of amygdaloid efferents was first described by Fox in 1940 as consisting of a diffuse

system of medially projecting fibers terminating in the whole rostrocaudal extent of the ventral hypothalamus, the lateral preoptic region, and entopeduncular nucleus and the basal ganglia.

b. Fornix

The fornix is the only known efferent hippocampal connection arising, according to Allen (1948), from all the pyramidal cells of the hippocampus and also from isolated pyramidal cells of the polymorphic layer of the dentate gyrus. More recently this tract has been shown to receive cingulate gyrus efferents (Mitchell, 1953). Up to 10 years ago the fornix was considered to terminate mainly in the mammillary bodies, with a minor projection (precommissural fornix) passing rostral to the anterior commissure to terminate in the septum. The more recent experimental anatomical studies of Sprague et al (1961), Guillery (1956) and Nauta (1958) in tracing degeneration following various fornical lesions, have suggested the following,

i. The fornical projections are ipsilateral but for a few fibers that project, without hypothalamic synapse, into the midbrain via the supramammillary decussation.

ii. In the cat 30 per cent of the fornix is precommissural, terminating mainly in the septum. Two-thirds of the postcommissural fibers terminate in the basal and intermediate parts of the medial mammillary nucleus. The other one-third of the postcommissural fornix is distributed diffusely to hypothalamic nuclei and, without hypothalamic synapse, to the midbrain. The connections of this one-third postcommissural fornix are two-way.

iii. The higher the brain in phylogeny, the greater the ratio of post to precommissural fornix, and the greater the ratio of postcommissural fibers terminating in the medial mammillary nucleus to those terminating in the hypothalamus and midbrain.

c. Medial Forebrain Bundle

The origin and course of this tract were described above. It might here be stressed that its connections are two-way and that its fibers that terminate in the midbrain, without hypothalamic synapse, are not of septal origin.

d. Septum

Since this structure has intimate relations with the hypothalamus and has been implicated in the production of shivering (Stuart, 1961), its anatomy is here briefly reviewed. The term "septum" designates that part

of the anteromedial wall of each cerebral hemisphere that is ventral to the corpus callosum, dorsal to the olfactory tubercle and medial to the lateral ventricle. The precommissural septum is rostral to the anterior commissure, and the postcommissural septum is dorsal and immediately caudal to this commissure. It is more developed in lower mammals, the human vestige being the septum pellucidum that is developed from the postcommissural septum. The whole septum might well be termed "gray" in that its cells and fibers are diffusely mixed, but sufficient fiber tract "clear" zones exist to permit a separation of medial and lateral septal cell complexes and a further demarcation of each of these complexes into specific nuclei as follows.

i. Nuclei of the Medial Septal Cell Complex. A continual line of medial septal gray can be traced from the olfactory tubercle to the dorsal surface of the anterior commissure. This line contains cells from the anterior continuation of the hippocampus that have been described in the opossum (Gray, 1925), rat (Gurdjian, 1925), and rabbit (Young, 1936), which by projection over the rostral genu of the corpus callosum connect the cingulate gyrus with the rostral septum. The cells are small and pyramidal. The medial septal nucleus, also in the rostral septum, occupies the first free edge of the septum along the ventral fissure. Rostrally it is bounded by the olfactory tubercle, caudally by the nucleus of Broca's diagonal band. As shown in both cat (Fox, 1940) and opossum (Gray, 1925), the cells of the more rostral portion of the nucleus are smaller than those of the more caudal portion but there is no sharp demarcation between such cells. Irregular oval shaped cells of the nucleus of Broca's diagonal band connect the medial edge of the midseptum with the basal brain immediately rostral to the medial forebrain bundle. The nucleus bifurcates at its basolateral aspect into a ventral amygdala and a globus pallidus projection, the latter sometimes called the nucleus of the ansa lenticularis. The triangular nucleus is wedged between the descending columns of the fornix, immediately dorsal and rostral to the anterior commissure. The septo-hippocampal nucleus extends from the cells of the anterior continuation of the hippocampus rostrodorsally to the triangular nucleus caudoventrally. This nucleus, allegedly the equivalent of the primordial hippocampus of the turtle (Johnson, 1915) and alligator (Crosby, 1917), is but a vestige in the cat (Fox, 1940), but is related to a corresponding structure in the human embryo .

ii. Nuclei of the Lateral Septal Cell Complex. This complex extends from the junction of olfactory tubercle and anterior olfactory nucleus rostrally to the hippocampal commissure ventrally, and in its anterior-posterior extent is divided into accumbens nucleus, lateral septal nucleus, septo-fimbria nucleus and bed nucleus of the stria terminalis and anterior commissure. The accumbens nucleus is really that portion of the anterior head of the caudate nucleus that is medial to a sagittal plane

passing through the ventral tip of the anterior horn of the lateral ventricle. As such it lies within the septal region of the forebrain, its dorsomedial cells in continuity with the lateral septal nucleus, but it is a basal ganglionic rather than a septal structure. The lateral septal nucleus, occupying the entire horizontal length of the septum, is immediately adjacent to the medial wall of the lateral ventricle. Anteriorly its cells are dorsolateral to those from the anterior continuation of the hippocampus, here beginning rostral to the medial septal nucleus. Hence its cells are continuous rostrally making a dorsal arch over the medial septal nuclei but more caudally the lateral septal nuclei are separated by the descending columns of the fornix. The septo-fimbria nucleus is the caudal continuation of the lateral septal nucleus and is distinguished from it solely on the basis of its projections to the septo-habenular tract in the opossum (Gray, 1925). This nucleus lies along the lateral margin of the descending column of the fornix caudally but rostrally it arches over this column to meet its contralateral brother. The bed nuclei of the stria terminalis and the anterior commissure occupy a region bounded medially by the medial septal nucleus, laterally by the lateral septal nucleus, dorsally by the triangular nucleus and ventrally by the preoptic region.

As mentioned above, the classical separation of the septum into medial and lateral divisions is a somewhat arbitrary demarcation in terms of cellular discontinuities. The division appeared in the literature as a result of Crosby's 1917 report that in the alligator septum "the medial nucleus is a way-station for ascending impulses going toward the hippocampus and lateral nucleus is a similar station for descending impulses from the hippocampus." These observations of septal fiber connections were subsequently accepted by Gray (1925) for the opossum and Young (1936) for the rabbit. However, Fox (1940) has pointed out that, at least in the cat, "the septal nuclei are more than way-stations in the path of the fornix fibers." He reported that lateral septal nuclei receive impulses from hippocampus, olfactory stria and neocortex rostrally and the hypothalamus caudally, and project them to the accumbens nucleus and the caudate-putanem complex of the basal ganglia from which there are projections back to the medial efferents to the hippocampus and hypothalamus. More recently Nauta (1958) has demonstrated two-way septal terminations with the hypothalamus in which the septal terminations are common to both medial and lateral regions and the hypothalamic terminations are in both anterior and posterior regions. He additionally proved existence of direct two-way septal connections with the hippocampus, and the habenulum of the thalamus, but none with the midbrain that did not involve hypothalamic relay. Mettler (1947) has shown anatomically that areas 9 and 11 of the frontal cortex project to the septum and this has been confirmed electrophysiologically by Heath and his co-workers (Heath, 1953). There are no known connections between the septum and the anterior temporal cortex based on anatomical evidence but such are indicated by electrophysiological studies of Jasper and his co-workers (Ajmone-Marsan and Stoll, 1951; Stoll et al, 1951).

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In summary it would appear that the septal region of the fore-brain of animals lower than man receives afferents from the midbrain, thalamus and hypothalamus caudally and from the hippocampus, amygdala, olfactory bulb, basal ganglia, forebrain, neocortex and anterior temporal cortex rostrally. Direct septal efferents have been demonstrated to all the above structures but the midbrain and anterior temporal cortex. No study has ever proved conclusively that any of the above mentioned pathways involve relays through any specific region or individual nucleus of the septum and as such any acceptance of the demarcations between the above mentioned nuclei cannot, at this stage, be based on anatomical data. With respect to neural regulation of shivering the most striking aspect of septal anatomy is Nauta's finding that following a medial and/or lateral septal lesion, there is independent degeneration in both the anterior and posterior hypothalamus. This suggests the presence of septal cells in very close juxtaposition whose neurons diverge to the anterior and posterior hypo-thalamus. However, on the basis of Nauta's work no finer localization of the termination of these connections can be made.

e. Orbito-Hypothalamic Connections

As recently reviewed by Gloor (1956), the orbito-frontal cortex and the frontal cortex of area 6 have direct connections mainly with the ventromedial hypothalamic nucleus (Beck et al, 1951; Clark and Meyer, 1950). Connections also exist between these frontal regions and the supra-optic and paraventricular nuclei of the anterior hypothalamus and the medial mammillary nucleus of the posterior hypothalamus (Ban and Omakai, 1959; Meyer, 1949; Bard, 1961; Adey and Lindsley, 1959). The evidence in these five papers clearly suggests that such connections involve no intermediary synapse between cortex and hypothalamus and in four of these papers there is no mention of whether or not the septum was implicated in the course of these connections. In one of Meyer's (1949) reports, evidence was pre-sented of hypothalamic but not septum pellucidum degeneration in two patients who died within 11 days of frontal leucotomy. It would thus appear that connections between the frontal cortex and the hypothalamus involve no intermediary septal synapse but may or may not stream through the septal region of the forebrain.

In summarizing afferent telencephalic connections with the hypothalamus it is obvious that the phylogenetically older cerebral structures (hippocampus, amygdala, septum, olfactory bulb) have a greater number of better defined pathways to the hypothalamus than does the phylogenetically younger neocortex. However, it is also evident that both these telencephalic divisions send projections to the hypothalamus via the medial forebrain bundle and at least some of the neocortical projections involve a septal synapse and/or course.

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D. Ontogenetic and Comparative Aspects of Hypothalamic Anatomy

Such aspects have been well, but not recently, reviewed by Gilbert in 1935, Papez in 1939, Rose in 1942 and Cooper in 1950 with respect to ento-genetic aspects, and by Boon (1938) and le Gros Clark et al in 1938 and Crosby and Woodburne in 1939 with respect to phylogenetic aspects. I reviewed the above material in the hope that a comparison of a hypothalamic anatomy in the same animal before and after the ontogenetic appearance of shivering and of the anatomy of shivering and nonshivering animals might delimit hypothalamic regions involved in the production of shivering. If such were the case it would be analogous to evidence that the relative development of the hypophyseal-portal circulation has functional counter-parts. However, at least with respect to shivering and temperature regula-tion, this approach has not proved helpful. In species lower than the reptilian stage there are reports of anatomical aberrations related to the relative extent of the tuberal region which is conspicuous in fish and incon-spicuous in amphibians. In all species from cyclostomes to mammals, the hypothalamus is evident, contains neurosecretory cells, has a higher vascu-larity than the rest of the brain and clear relationships to the pituitary gland. The most striking aspect of both the ontogenetic and phylogenetic development of the hypothalamus is that the mammillary bodies become larger and more differentiated and this is accompanied by similar increase in the size and compactness of the post-commissural fornix and mammillo-thalamic tract. Since this system is not implicated in the production of shivering it is of little value in furthering knowledge of shivering's neuro-genesis. It is true that in man the posterior hypothalamic nucleus is more differentiated and the relative size of its cells and the region they embrace is greater than in lower mammals, but no such distinction can be made between this region in the "non-shivering lizard" and the "shivering cat." Such negative conclusions with respect to the value of ontogenetic and com-parative hypothalamic anatomy in elucidating shivering's neurogenesis does not mean that such relations between comparative anatomy and function do not exist. Rather it might well be an expression that the data accumulated in this field of endeavor at the present time is too insufficient, and the technique of staining the small hypothalamic cells, embedded in such a dense neuropil of finely myelinated and unmyelinated fibers, too crude, to be informative.

In conclusion it must be stressed that no attempt was made here to distinguish between examination of intact neuro-anatomical material (clas-sical anatomy) and material in which degeneration was produced by destruc-tion of some specific portion of the brain (experimental anatomy). Such a distinction is requisite to a separation of two-way from one-way connections between neural structures. This brief and uncritical report certainly re-flects the current need for a definitive review of the anatomy of the hypothal-amus and its connections with emphasis on the integration of classical and recent experimental information.

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3. Anatomy
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